Generation of multiciliated cells in functional airway epithelia from human induced pluripotent stem cells.

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Public Summary:
Lung disease is the third highest cause for morbidity and mortality worldwide. Studies of human lung disease are currently limited by accessibility to the relevant patient tissues. The ability to take a skin cell and reprogram it into an induced pluripotent stem cell, a cell theoretically capable of generating any cell in the body, provides an invaluable tool for studying such lung diseases. We developed a step-wise differentiation protocol ending in an air–liquid interface to generate a pseudostratified polarized layer of endodermal-derived epithelial cells, the cells that reside in the respiratory tract. This layer includes secretory cells called Clara cells and goblet cells and multiciliated cells which generate flow in the fluid lining the lungs. The cells have forskolin-induced chloride currents sensitive to cystic fibrosis transmembrane regulator inhibitor 172, also important in maintaining the periciliary liquid layer. The development of this model will enable the future study of many lung diseases (especially those where defective cilia are involved, such as primary ciliary dyskinesia) that have been difficult to study in human models from a developmental perspective.

Scientific Abstract:
Despite therapeutic advancement, pulmonary disease still remains a major cause of morbidity and mortality around the world. Opportunities to study human lung disease either in vivo or in vitro are currently limited. Using induced pluripotent stem cells (iPSCs), we generated mature multiciliated cells in a functional airway epithelium. Robust multiciliogenesis occurred when notch signaling was inhibited and was confirmed by (i) the assembly of multiple pericentrin-stained centrioles at the apical surface, (ii) expression of transcription factor forkhead box protein J1, and (iii) presence of multiple acetylated tubulin-labeled cilia projections in individual cells. Clara, goblet, and basal cells were all present, confirming the generation of a complete polarized epithelial-cell layer. Additionally, cAMP-activated and cystic fibrosis transmembrane regulator inhibitor 172-sensitive cystic fibrosis transmembrane regulator currents were recorded in isolated epithelial cells. Our report demonstrating the generation of mature multiciliated cells in respiratory epithelium from iPSCs is a significant advance toward modeling a number of human respiratory diseases in vitro.

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